

Remarks/Arguments

Claims 39-43 are pending in this application. Claim 39 has been amended for clarity. All claims remain rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The rejection is respectfully traversed.

Rejections under 35 USC § 112, first paragraph - enablement

Claims 39-43 were rejected under 35 USC 112, first paragraph, for lack of enablement. The Examiner asserts that the "activation of a mixed lymphocyte reaction is not widely used as an assay for immunotherapeutics....it is widely used for determining histocompatibility, not for identifying immunostimulatory agents for therapeutic purposes or as targets." Applicants respectfully disagree.

Without acquiescing to the propriety of this rejection, solely in the interest of expediting prosecution in this case, Applicants submit a declaration by Sherman Fong, Ph.D. of Genentech, Inc., an expert in the field of Immunology and co-inventor of the present application, and supportive references to show that, besides being useful "for determining histocompatibility," the MLR assay has other uses, for example, in detecting immunostimulatory activities of molecules like PRO335.

As stated in Current Protocols in Immunology, Vol. I, Unit 3.12 by Richard Coico (Exhibit A), a reference popularly used by people skilled in the art of immunology/immunotherapeutics:

"A number of agents can specifically or nonspecifically induce T cell activation, resulting in cytokine production, cytokine receptor expression, and ultimately proliferation of the activated T cells" (see page 3.12.1, first paragraph).

Further, the Fong Declaration explains,

"The MLR assay of the present application is designed to measure the ability of a test substance to "drive" the dendritic cells to induce the proliferation of T-cells that are activated, or co-stimulated in the MLR, and **thus identifies immune stimulants that can boost the immune**

system to respond to a particular antigen that (m)ay not have been immunologically active previously" (Emphasis added).

Thus, the MLR assay is a well accepted and useful assay for identifying immunostimulants, which are important and are very desirable, for example, in the treatment of cancer or in enhancing the effectiveness of previously identified treatments for cancer. Supportive evidence for such teachings also come from the art; for example, as Steinman *et al.* (Exhibit B) states "...**medicine needs therapies that enhance immunity or resistance to infections and tumors** (page 1, column 1, line 7; emphasis added)". Further Peterson *et al.* (Exhibit D) show that, the immune stimulant, IL-12, was successfully used in a cancer vaccine trial to treat melanoma. As Dr. Fong explains regarding the IL-12 melanoma trial:

"Due to the immune stimulatory effect of IL-12, **the treatment provided superior results** in comparison to earlier work, where the patients' own dendritic cells were prepared from peripheral blood mononuclear cells (PBMCs) treated with antigens, then cultured *in vitro* and returned to the patient to stimulate anti-cancer response" (Emphasis added).

The Fong Declaration also explains how the MLR reaction of the instant application was performed using peripheral blood mononuclear cells (PBMCs) and allogenic, pre-treated (irradiated) PBMCs, which predominantly contain dendritic cells, and clearly states that:

"A PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is expected to have the type of activity exhibited by IL-12 and would find practical utility **as an immune stimulant**" (Emphasis added).

Based on a positive result for PRO335 in the instant MLR assay, one skilled in the art would know that the immunostimulant PRO335 is useful in boosting the immune system, for example, in treating/combating diseases like melanoma, or HIV infection. In this regard, Applicants respectfully remind that the Examiner that the skilled artisan in the field of Immunology and Immunotherapeutics, at the effective filing date of September 17, 1998, would likely be a person with a Ph. D. or M.D. degree, sometimes both, with extensive experience. Based on the instant

disclosure that teaches how to make PRO335 and its antibodies, the MLR assay results and the knowledge in the art, the skilled person would routinely know "how to make and use" the instant immunostimulants without undue experimentation. Accordingly, the instantly claimed antibodies to PRO335 are useful as "immunosuppressants" to treat diseases like lupus, etc. and such utilities would readily be apparent to one skilled in the art.

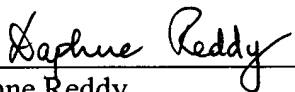
Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any additional fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C47). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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